Radiation Response of Neural Precursor Cells

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Radiation-induced CNS damage involving significant tissue destruction generally occurs after relatively high radiation doses like those used in radiotherapy, and oligodendrocytes and capillary endothelial cells have been implicated in the pathogenesis of such injury. However, less severe morphologic injury leading to cognitive dysfunction can also occur after irradiation, and it has been suggested that the hippocampus, a critical component of the medial temporal lobe memory system, may be involved. Because hippocampal neurogenesis occurs continuously in the subgranular zone (SGZ) of the dentate gyrus, cells responsible for the production of hippocampal neurons may constitute a 'target' for radiation-induced cognitive impairment. Hippocampal neurogenesis involves neuronal precursor cells whose progeny migrate into the granule cell layer, develop granule cell morphology and neuronal markers, and connect with their target area, CA3. Recent studies have shown that reductions in the number of newly generated neurons within the dentate gyrus result in a decrease in hippocampal-dependent memory. It seems reasonable, therefore, that any agent that damages neuronal precursor cells and/or their progeny, such as ionizing irradiation, could have an impact in specific memory functions.

Studies from our lab have specifically addressed the radiation response of the neuronal precursor cells in the SGZ of the rodent dentate gyrus and neural stem cells in another neurogenic area of the forebrain, the subependymal zone. Our studies have shown that in rats and mice, proliferating neuronal precursor cells and their undifferentiated progeny are very sensitive to radiation, undergoing apoptosis 6-12 hours after x-ray doses as low as 0.5 Gy. In response to this acute cell loss, surviving stem/precursor cells begin to divide, but appear unable to re-establish normal proliferative levels in these areas. At least for 6 months following exposure, there is a dose-dependent reduction in the number of proliferating cells in both neurogenic regions. It is not clear if surviving cells are unable to repopulate or if they have not received the proper signal(s) to do so. Although our experimental data show an early and significant reduction in proliferation in the SGZ, cognitive deficits generally appear after many months. The events associated with the slow development of cognitive changes have not been elucidated, but they are consistent with a loss of cellular input (i.e. precursor cell proliferation) into a population of neuronal cells that decreases slowly over time.

With the apparent relationship between hippocampal neurogenesis and associated memory formation, we propose that a radiation-induced reduction in neurogenesis plays an important role in the development of cognitive impairments after irradiation. It is our contention that low doses of irradiation, particularly from damaging high LET particles, can result in significant depletions of neural precursor cells and immature neurons in the dentate gyrus of the hippocampus. The apparent lack of ability of these cells to recover may result in a slowly developing loss of cognitive function that could have a significant impact in individuals exposed to such radiation.

- Neuronal Precursor cells (NP) may constitute another "target" for radiation damage in the CNS.

- NP reside in two areas in the mammalian forebrain where they participate in the process of neurogenesis – production of neurons, astrocytes and oligodendrocytes.
  - Subependymal zone (SE) lining the lateral ventricles.
  - Subgranular zone (SGZ) of the dentate gyrus.

- NP produce cells that migrate away and differentiate into mature phenotypes.
  - Cells from the SE migrate to the olfactory bulb.
  - Cells from the SGZ migrate into the dentate granule cell layer.

- Radiation induces significant apoptosis in both the SGZ and SE 6-12 hours after exposure.

- In both the SGZ and SE the dose response curves for apoptosis are very steep, going from zero to maximum values over 1 to 3 Gray of X-rays.

- Proliferating NP's and their progeny, which are just beginning to differentiate, appear to be the most susceptible cellular elements to ionizing irradiation.

- After the initial apoptosis, surviving stem/precursor cells in the SE and SGZ attempt to repopulate the regions.

- The stem/precursor cells are unable to repopulate the SE and SGZ, at least for 4-6 months after irradiation, and the depression of neurogenesis is radiation dose dependent.

- It is unknown whether the cells are unable to repopulate or do not receive the appropriate signal(s) to carry out the repopulation.

- The stem/precursor cell population constitutes a sensitive population of cells in the CNS. Their depletion may have a significant impact to individuals exposed to high LET radiation because their progeny develop into neurons in discrete areas of the brain.

- In particular, cells from the SGZ differentiate into granule cell neurons. Because the dentate gyrus has been shown to be involved in memory functions, radiation-induced effects on neurogenesis may be manifest as neurocognitive impairment.